REMARKS

Claims 1-36, 38-46, and 48-55 are currently pending in this application. Claim 37 has been cancelled. Claim 47 is withdrawn from consideration. Claims 1-46 and 48-55 stand rejected. Claims 1, 2, 22, 40, 41, 46, 48, and 50 are currently amended. No new matter has been introduced by these amendments.

Claims 1, 2, 22, 40, 41, 46, 48, and 50 have been amended for clarification and the correction of typographical/grammatical errors. Support may be found throughout the specification. No new matter has been introduced by these amendments.

35 U.S.C. §103 Rejections

Claims 1-46 and 48-55 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Impraim, et al. (USPN: 6,228,578) in view of Nathan, et al. (USPN: 6,057,099) and Shah, et al. (USPN: 5,629,156). Applicants respectfully traverse the Examiner's rejection.

The Examiner in this rejection has lumped all of the claims into one group, citing bits and pieces of the various prior art references, and then summarily concluded that all of the pending claims are obvious. As an initial matter, applicants wish to point out that the pending claims vary in scope and the patentability of each claim must be considered independently of the others. Therefore, in responding to the Examiner's rejection, applicants have separated out groups of claims having common features in order to clearly point out the distinguishing features of the claimed inventions as compared to the cited prior art.

Regarding claims 22-31 and 40-45, the Examiner alleges that Impraim in view of Nathan and Shah renders these claims obvious. The invention recited in these claims utilizes a

capture sequence probe, a signal sequence probe, a target nucleic acid, and an antibody specific for hybrids for detecting a target nucleic acid. The Examiner has selected the Impraim reference as the primary reference for the alleged obviousness rejection. The Impraim method comprises utilizing a single RNA probe which hybridizes to a target nucleic acid forming a DNA-RNA hybrid; capturing the hybrid using an antibody specific for the DNA-RNA hybrid; removing non-hybridized probe by digesting the excess probe with RNase; and detecting the DNA-RNA hybrid. Because Impraim uses only one type of nucleic acid probe instead of at least two as is the case of the instant invention, the Impraim method does not teach or suggest the use of four components, *i.e.,* a capture sequence probe, a signal sequence probe, a target nucleic acid, and an antibody specific for hybrids for detecting the target nucleic acid. Thus, the Impraim method does not teach or provide guidance for the use of two different nucleic acid probes for detecting a target nucleic acid. Rather, Impraim suggests that one nucleic acid probe, *i.e.*, the RNA probe, is sufficient for detecting the target nucleic acid.

The Nathan reference describes a method analogous to the polymerase chain reaction (PCR) which is a completely different technique than the claimed method. In particular, Nathan uses transcription and RNA amplification steps for detecting the resulting transcription reaction product, which indirectly detects the presence or absence of the assayed target nucleic acid. Briefly, a first oligonucleotide and a second oligonucleotide are hybridized to a target nucleic acid, ligated, and followed by transcription. The transcription reaction product of Nathan is then amplified to obtain large quantities of the transcript for detection (*See*, Nathan, Fig. 1). Although the ligation step is generally described as optional, ligation is required if the first and second oligonucleotides are complementary to only a part of the entire length of the target nucleic acid sequence, because transcription will not otherwise occur due to the gap between the

first and second oligonucleotides. Furthermore, ligase forms a phosphodiester bond between the 5' phosphate of one strand of DNA and the 3' hydroxyl of another, so the first and second oligonucleotides need to be ligated together in contrast to the instant invention. The CSP and the SSP of the instant invention are selected to hybridize to regions of the target within 50,000 bases of each other, and ligation is not required or needed to perform the claimed method. Contrary to the instant invention, Nathan's first oligonucleotide does not function as a signal sequence probe (SSP), but rather serves as a template for transcription as described above. Furthermore, the first and second oligonucleotides of Nathan, once ligated essentially form and function as one nucleic acid probe instead of two separate probes. Because Nathan's first and second oligonucleotides do not resemble or function like the capture sequence probe (CSP) and signal sequence probe (SSP) of the claimed invention, and the Nathan method comprises transcription, amplification, and detection of the resulting transcription product, Nathan does not teach or suggest the method of the instant invention.

The Examiner has cited Nathan as teaching the use of blocker probes, which are not a feature of these particular claims. Therefore, Nathan does not add any further teaching to Impraim to reach the invention claimed in claims 22-31 and 40-45. For example, Impraim uses a single nucleic acid probe for capture and detection. By ligating the two probes, Nathan also teaches that a single probe is best for detection and capture. Therefore, a combination of the Impraim and Nathan references do not teach or suggest the invention as recited in claims 22-31 and 40-45.

The Examiner has further combined Shah with Impraim and Nathan to assert that the method of hybridizing a target nucleic acid to a capture probe and a signal sequence probe,

and detecting the bound hybrid as recited in claims 22-31 and 40-45 is obvious. Applicants respectfully disagree with this rejection.

Briefly, the Shah reference describes a method of capture-release, where a target is hybridized with a first capture probe and a detector probe on a target molecule, where the capture probe directly binds the resulting nucleic acid to a solid support. After target capture, the target is released from the first solid support under conditions where the first capture probe remains bound to the solid surface because it has a higher affinity for the solid support than the target, and the labeled detector probe remains bound to the target. The target-detector probe complex is then exposed to a second capture probe which forms a new complex with the target (*see*, Shah, col. 3, ln. 65 – col. 4, ln.10). This function requires that the second capture probe be complementary to the target sequence and that the detector probe be labeled with a detectable moiety (col. 1, lns. 30-32). The Examiner equates "detector probe" to the signal sequence probe (SSP) of the instant invention. However, the SSP of claims 22-31 and 40-45 is not detectably labeled.

The Examiner further cites Shah for the teaching that dA-tailed probes and capture probes can be used in the assay of Impraim. However, Shah teaches that two different capture-type probes are necessary and that each must bind to the target nucleic acid and a solid support, in contrast to the claimed methods. Therefore, combining Impraim with Nathan and Shah does not reach the methods of claims 22-31 and 40-45, in that neither Nathan or Shah teach or suggest the use of one signal sequence probe and one capture probe wherein the signal sequence probe is unlabeled. One skilled in the art at the time of the instant invention could not reach the claimed methods by applying a combination of the cited references. Therefore,

applicants respectfully request reconsideration and withdrawal of this §103 rejection for the above reasons.

With respect to claims 1-21, 37-39, 46, and 48-49, the Examiner alleges that Impraim in view of Nathan and Shah renders these claims obvious. However, even the Examiner admits that Impraim does not "teach blocker probes, immobilization of the probes and use of bridge probes or dT-tailed probes [sic; dA-tailed probes]" (Office Action-page 4, ¶5). The fact that Impraim contains negative teachings which would discourage and deter a person of ordinary skill in the art from using blocker probes is further evidence of non-obviousness. *Mobil Oil Corp. v. W. R. Grace & Co.*, 367 F. Supp. 207, 180 U.S.P.Q. 418, 452 (Conn. 1973). Specifically, Impraim suggests the use of RNase to digest non-hybridized excess RNA probe instead of using blocker probes in contrast to the instant invention which uses blocker probes that bind excess non-hybridized capture sequence probes.

The Examiner cites Nathan as teaching the use of blocker oligonucleotides for reducing background signal, and contends that it would have been obvious for a skilled artisan to modify the method of Impraim with the step of adding blocker probes as taught by Nathan. Assuming arguendo that the Nathan reference uses the blocker probes as claimed in the instant invention, the Examiner presented no line of reasoning as to why the skilled artisan reviewing only the combined teachings of the references would have found it obvious to selectively pick and choose various elements from the references relied upon to arrive at the claimed invention. A person having ordinary skill in the art would not have found it obvious to selectively pick and choose the use of two nucleic acid probes, a blocker probe, and a non-transcription method from the cited references so as to arrive at the claimed invention without using the claims as a guide.

Ex parte Clapp, 227 U.S.P.Q. 972 (B.P.A.I. 1985). This is especially true in view of Impraim which teaches away from using multiple nucleic acid probes and blocker probes.

There is no motivation or guidance in the cited publications for one skilled in the art to use the claimed blocker probes in the claimed method of detecting a target nucleic acid. Further, the Examiner has improperly used hindsight to reach the present invention from the cited art (which do not teach or make obvious applicants' invention) as there is no motivation to combine these particular references in this particular fashion. The Nathan reference does not remedy the insufficiencies of the Impraim method to result in the claimed method of detecting a target nucleic acid blocker probes. In fact, the combination of Impraim and Nathan specifically fails to provide motivation for a skilled artisan to use a capture sequence probe, a signal sequence probe, and a blocker probe for detecting a target nucleic acid according to the claimed invention. Therefore, a combination of Impraim and Nathan does not teach or suggest adding blocker probes to the Impraim method, nor does this combination teach or suggest the methods recited in claims 1-21, 37-39, 46, and 48-49. Therefore, applicants respectfully request reconsideration and withdrawal of this §103 rejection.

Furthermore, adding the Shah reference does not remedy the defects of Impraim and Nathan. The method described by Shah also does not use blocker probes as used in the claimed invention. In fact, Shah teaches away from the use of blocker probes, and uses a repeated capture-release method for reducing background (Col. 7, lines 30-61). Both Impraim and Shah teach away from using blocker probes in favor of RNase and a capture-release method, respectively. Impraim and Shah in combination do not teach or suggest the claimed method, and even with Nathan's "blocker" probes, the combination of references still also does not result in

the method of detecting a target nucleic acid using blocker probes to reduce background recited in claims 1-21, 37-39, 46 and 48-49.

In summary, Impraim teaches that the use of only one type of RNA probe is sufficient for detecting target nucleic acid. Multiple probes, such as capture sequence probes and signal sequence probes, are not taught or suggested by the Impraim reference. Also, because Impraim teaches how to reduce background noise by using an RNA digestion enzyme, one skilled in the art would not be motivated to use the probes of Nathan in combination with the method of Impraim. Moreover, both Impraim and Shah teach away from using blocker probes in favor of RNase and a capture-release method, respectively.

Therefore, none of the references when viewed in combination, teach or suggest the methods of claims 1-21, 37-39, 46, and 48-49 as a whole. In applying the cited references, the skilled artisan would not be able to generate the claimed method, which detects complexes of double-stranded hybrids comprising a signal sequence probe, a capture sequence probe, and a target nucleic acid by using the signal sequence probes, the capture sequence probes, and the blocker probes of the claimed invention. Thus, applicants respectfully request reconsideration and withdrawal of the §103 rejection to claims 1-21, 37-39, 46, and 48-49 in view of these arguments.

With respect to claims 50-55, the Examiner has combined Impraim and Nathan with Shah and alleges that the Shah reference shows the "use of dA-tailed probes (bridge probes) which bind to both target and dT derivatized supports." Applicants respectfully disagree with this rejection.

Contrary to the Examiner's pending rejections, Shah does not teach or suggest "bridge probes" as taught by the present invention. The Shah reference does not use bridge probes that function as those described in the instant invention. Shah's bridge probes serve to capture the target to solid supports. The dA-tailed probes of Shah act as a bridge between a solid support and a target nucleic acid, *i.e.*, "bind to both target and dT derivatized supports" (Shah; col. 8, lns. 48-50).

The instant invention as recited in claims 50-55 includes the step of using bridge probes to enable the detection of the target by "bridging" the target nucleic acid and signal sequence probe. The signal sequence probe (SSP) does not bind the target directly, but rather the bridge probe binds to both the SSP and the target nucleic acid sequence forming a bridge (Figs. 6B-D). Applicants respectfully point out that the bridge probes of the invention do not bind to solid supports AT ALL. The function of the instant bridge probe is to allow the SSP to indirectly bind to the target nucleic acid. In fact, capture sequence probes of the instant invention are used to bind the target nucleic acid to a solid support, not bridge probes. It appears that the Examiner has confused bridge probes and capture sequence probes of the instant invention.

The Examiner contends that the instant claims do not recite any structural limitation to the bridge probes. Applicants respectfully disagree with the Examiner's contention. Specifically, applicants direct the Examiner's attention to Claim 50 which states that the capture sequence probe and bridge probes hybridize to regions of the target nucleic acid, and the signal sequence probe hybridizes to the bridge probe and does not hybridize to the target nucleic acid and the capture sequence probe. Whereas, in Shah, the "dA-tailed probes (bridge probes)" hybridize to the target nucleic acid. Therefore, Shah, as cited by the Examiner, does not teach or suggest bridge probes as recited in claim 50 and depending claims 51-55.

Neither Impraim nor Nathan remedy the defects of the Shah reference. Thus, the methods of Impraim and Nathan, in combination with Shah, do not make obvious the claims of the instant application reciting bridge probes. Therefore, the cited references in combination do not teach or suggest the claimed method as a whole. Reconsideration and withdrawal of the §103 rejection directed to claims 50-55 is respectfully requested for the above reasons.

Regarding dependent claims 7-8 and 28-29, the Examiner has further combined Impraim and Nathan with Shah to show that "the capture probe and the detector probe distance when hybridized to a target comprises less than 3.0 kb." Applicants respectfully disagree with this rejection. Claims 7-8 and 28-29 are dependent claims. Dependent claims are not obvious under 35 U.S.C. §103 if the independent claims from which they depend are non-obvious. *In re Fine*, 837 F.2d 1071, 1076, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). Applicants submit that, as the independent claims from which the dependent claims depend are believed non-obvious and allowable for at least the reasons discussed above, the dependent claims are believed non-obvious and allowable for at least similar reasons. Therefore, reconsideration and withdrawal of the §103 rejection to dependent claims 7-8 and 28-29 is respectfully requested in view of the reasons above.

Accordingly, the present invention as recited in independent claims 1, 2, 22, 40, and 50, and the claims depending therefrom is believed to be non-obvious and patentable in view of Impraim, Nathan, and Shah taken individually or in combination.

CONCLUSION

Based on the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

Applicants respectfully believe that the subject application is patentably distinguished over the art and that the claims are in condition for allowance. An action passing this case to issue is courteously urged.

In the event that the Examiner is of the opinion that further discussion of the application would be helpful, the Examiner is hereby respectfully requested to telephone the applicants' undersigned representative at (212) 415-8517 and is assured of full cooperation in an effort to advance the prosecution of the instant application and claims to allowance.

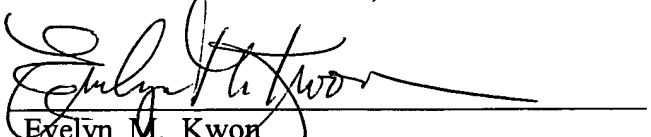
AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. 13-4500, Order No. 2629-4017. A DUPLICATE OF THIS DOCUMENT IS ATTACHED.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 2629-4017. A DUPLICATE OF THIS DOCUMENT IS ATTACHED.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

Dated: August 15, 2005

By: 
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